FIG. 1

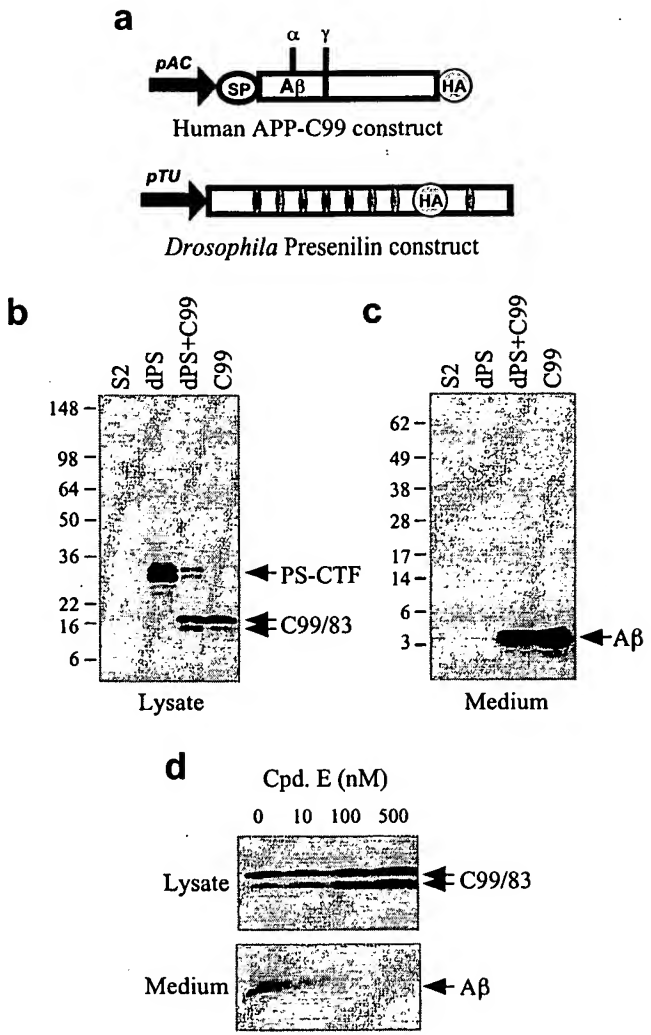

a
α
γ
pAC
SP
Aβ
HA
Human APP-C99 construct
pTU
HA
Drosophila Presenilin construct
b
S2
dPS
dPS+C99
C99
148
98
64
50
36
22
16
6
PS-CTF
C99/83
Lysate
c
S2
dPS
dPS+C99
C99
62
49
38
28
17
14
6
3
Aβ
Medium
d
Cpd. E (nM)
0 10 100 500
Lysate
C99/83
Medium
Aβ

FIG. 2

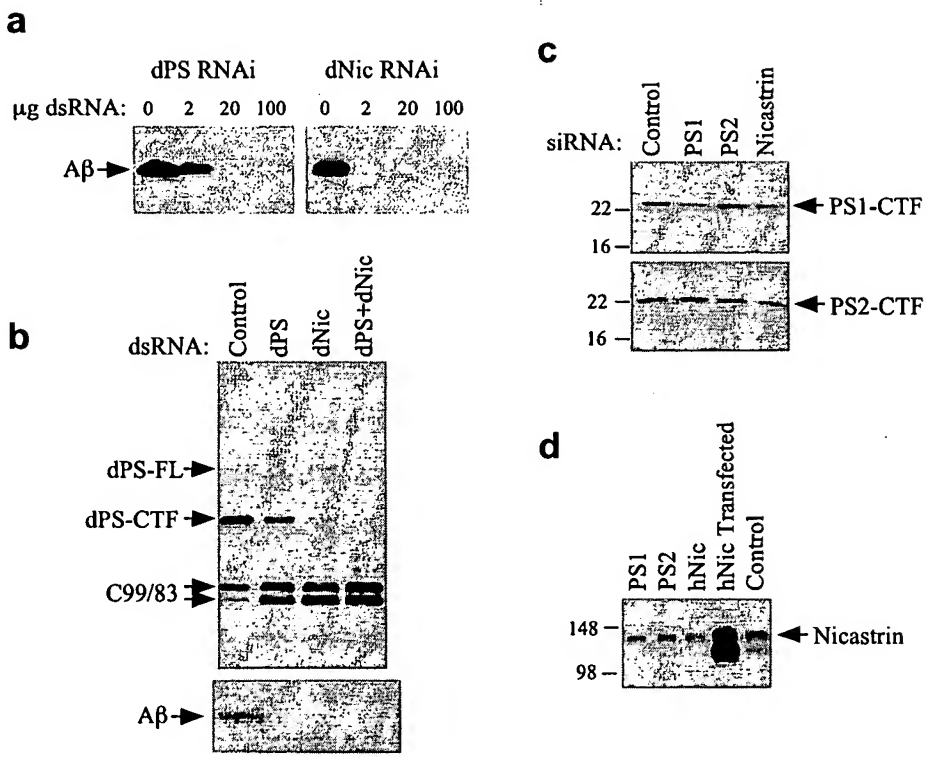

a
dPS RNAi
dNic RNAi
μg dsRNA: 0 2 20 100 0 2 20 100
Aβ
b
dsRNA: Control dPS dNic dPS+dNic
dPS-FL
dPS-CTF
C99/83
Aβ
c
siRNA: Control PS1 PS2 Nicastrin
22
16
PS1-CTF
22
16
PS2-CTF
d
PS1 PS2 hNic hNic Transfected Control
148
98
Nicastrin

FIG. 3

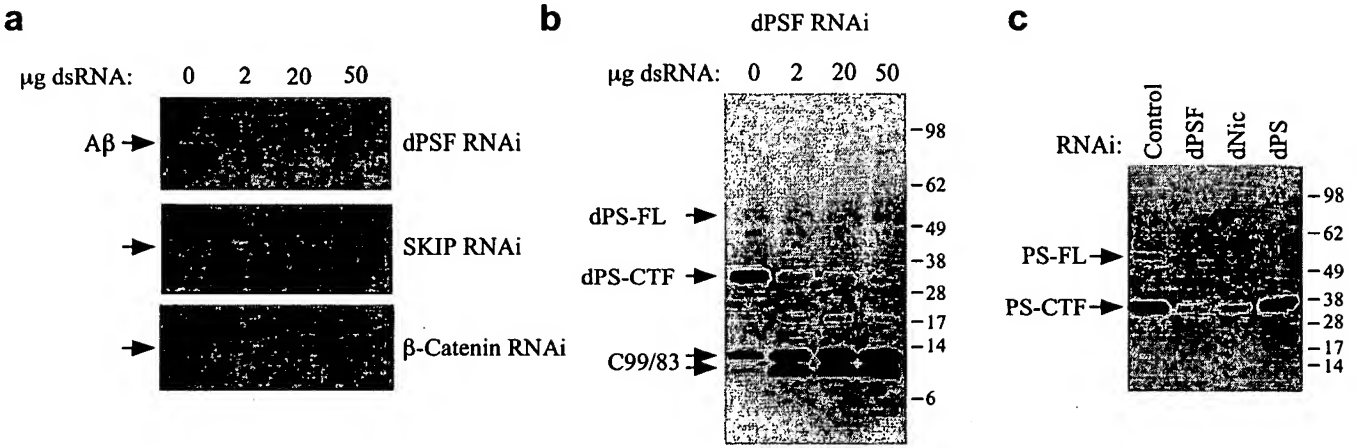

a
μg dsRNA: 0 2 20 50
Aβ
dPSF RNAi
SKIP RNAi
β-Catenin RNAi
b
dPSF RNAi
μg dsRNA: 0 2 20 50
dPS-FL
dPS-CTF
C99/83
98
62
49
38
28
17
14
6
c
RNAi: Control dPSF dNic dPS
PS-FL
PS-CTF
98
62
49
38
28
17
14

FIG. 4

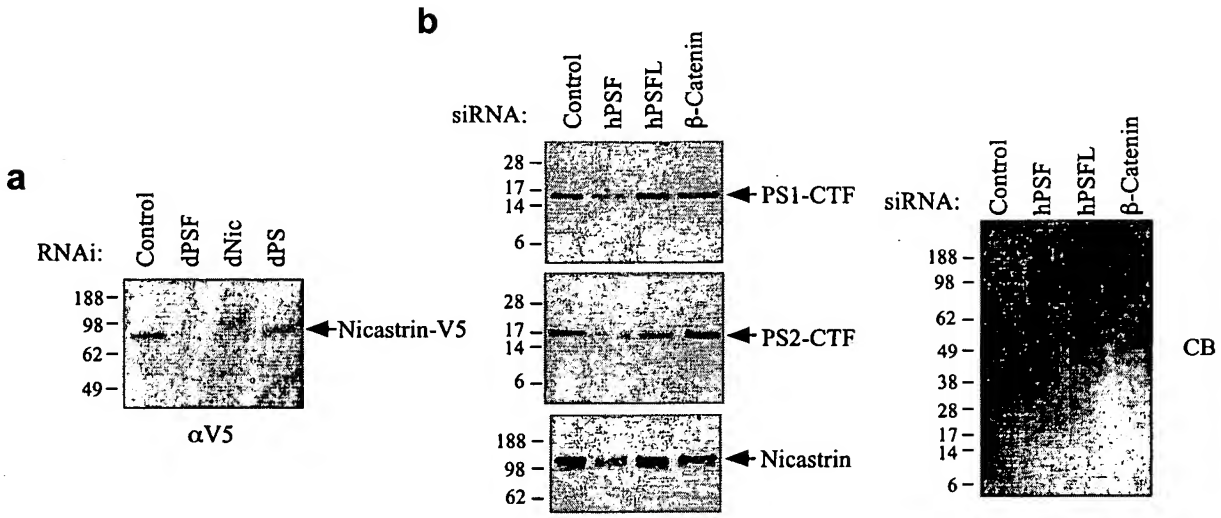

a
RNAi:
Control
dPSF
dNic
dPS
188
98
62
49
Nicastrin-V5
αV5
b
siRNA:
Control
hPSF
hPSFL
β-Catenin
28
17
14
6
PS1-CTF
PS2-CTF
188
98
62
Nicastrin
CB
38

FIG. 5

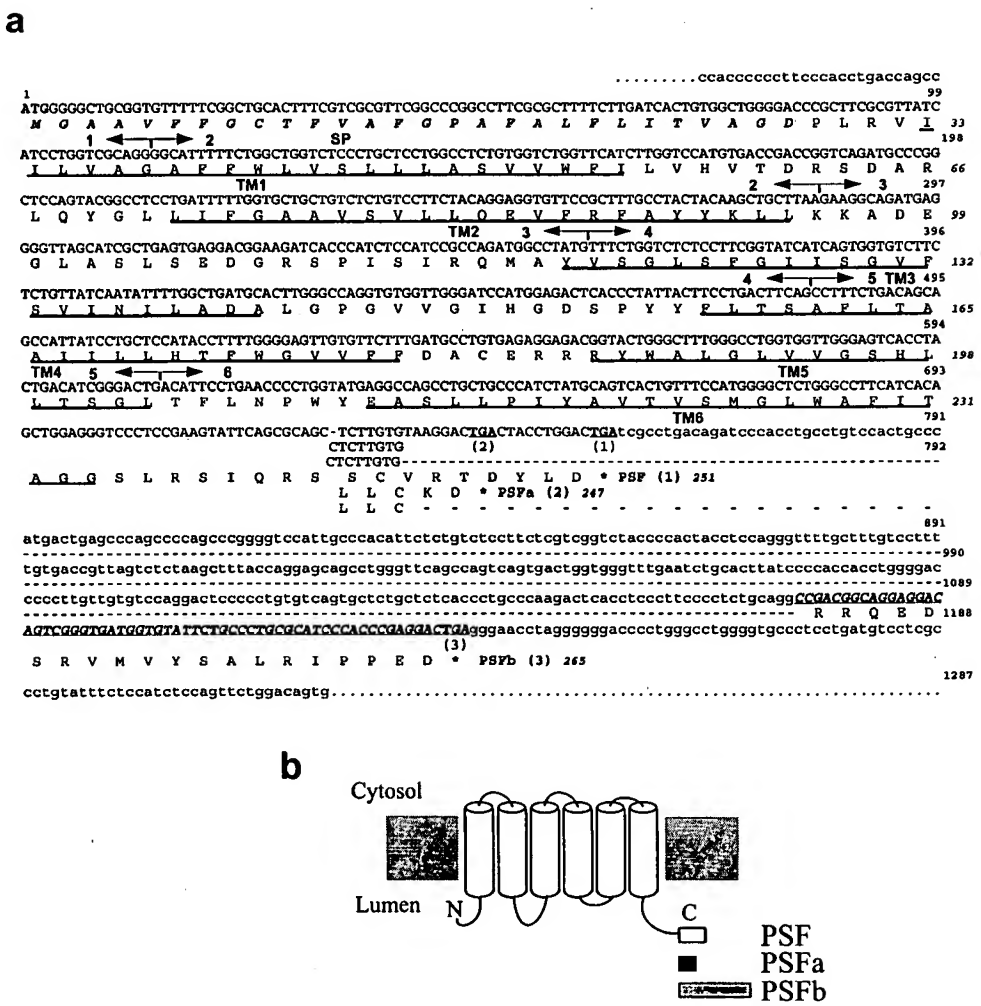
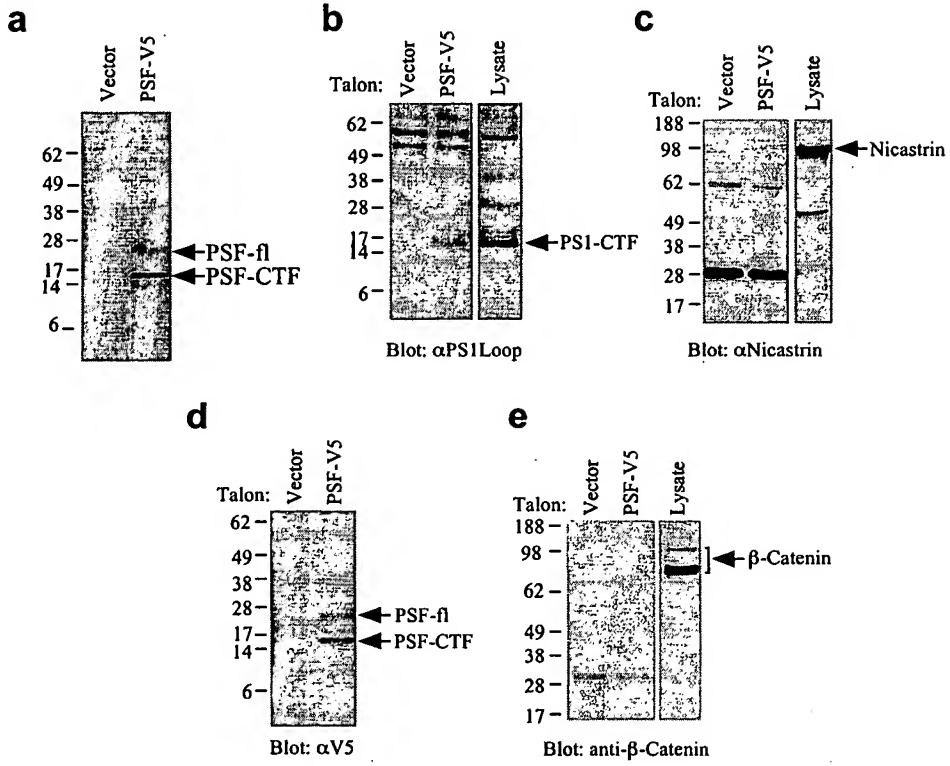

a
b
Cytosol
Lumen
N
C
PSF
PSFa
PSFb
c
Brain
Heart
Kidney
Spleen
Liver
Colon
Lung
Small Intestine
Muscle
Stomach
Testis
Placenta
PSF/PSFa
PSFb
Actin
Salivary
Thyroid
Adrenal
Pancreas
Ovary
Uterus
Prostate
Skin
PBL
Bone Marrow
Fetal Brain
Fetal Liver
PSF/PSFa
PSFb
Actin
d
Frontal Lobe
Temporal Lobe
Cerebellum
Hippocampus
Substantia Nigra
Caudate Putmen
Amygdala
Thalamus
Hypothalamus
Pons
Medulla
Spinal Cord
PSF/PSFa
PSFb
Actin

FIG. 6


a
Vector
PSF-V5
62
49
38
28
17
14
6
PSF-fl
PSF-CTF
b
Talon:
Vector
PSF-V5
Lysate
62
49
38
28
17
14
6
PS1-CTF
Blot: αPS1Loop
c
Talon:
Vector
PSF-V5
Lysate
188
98
62
49
38
28
17
Nicastrin
Blot: αNicastrin
d
Talon:
Vector
PSF-V5
62
49
38
28
17
14
6
PSF-fl
PSF-CTF
Blot: αV5
e
Talon:
Vector
PSF-V5
Lysate
188
98
62
49
38
28
17
β-Catenin
Blot: anti-β-Catenin

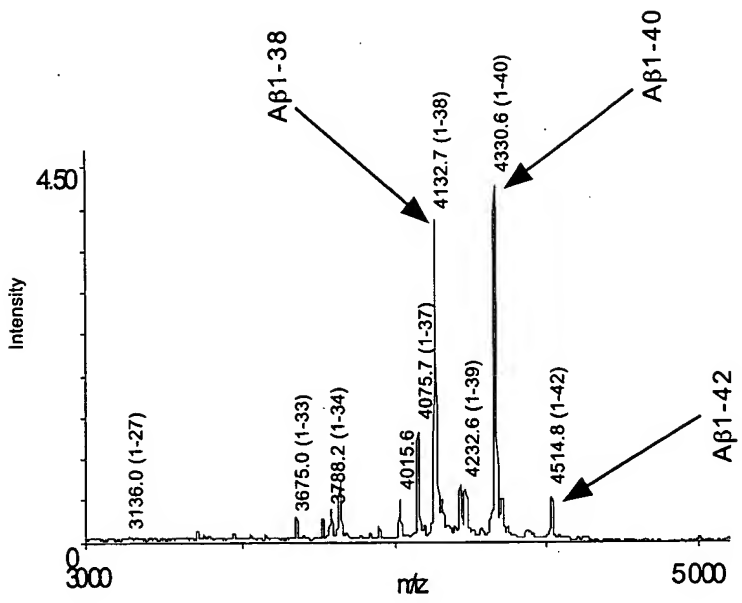

Aβ1-38
Aβ1-40
Aβ1-42
4132.7 (1-38)
4330.6 (1-40)
4075.7 (1-37)
4232.6 (1-39)
4514.8 (1-42)
4015.6
3788.2 (1-34)
3675.0 (1-33)
3136.0 (1-27)
4.50
Intensity
0
3000
m/z
5000

FIG. 7

CCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCCTTCCCACCTGACCAG
CCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTCGCGTTCGGCCCGGCCTT
CGCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTC
GCAGGGGCATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCA
TCTTGGTCCATGTGACCGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGA
TTTTTGGTGCTGCTGTCTCTGTCCTTCTACAGGAGGTGTTCCGCTTTGCCTACTA
CAAGCTGCTTAAGAAGGCAGATGAGGGGTTAGCATCGCTGAGTGAGGACGGAA
GATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTGGTCTCTCCTTCGGTAT
CATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTTGGGCCAGGT
GTGGTTGGGATCCATGGAGACTCACCCTATTACTTCCTGACTTCAGCCTTTCTGA
CAGCAGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATGCCTG
TGAGAGGAGACGGTACTGGGCTTTGGGCCTGGTGGTTGGGAGTCACCTACTGAC
ATCGGGACTGACATTCCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCATCTA
TGCAGTCACTGTTTCCATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCT
CCGAAGTATTCAGCGCAGCTCTTGTGTAAGGACTGACTACCTGGACTGATCGCC
TGACAGATCCCACCTGCCTGTCCACTGCCCATGACTGAGCCCAGCCCCAGCCCG
GGGTCCATTGCCCACATTCTCTGTCTCCTTCTCGTCGGTCTACCCCACTACCTCC
AGGGTTTTGCTTTGTCCTTTTGTGACCGTTAGTCTCTAAGCTTTACCAGGAGCAG
CCTGGGTTCAGCCAGTCAGTGACTGGTGGGTTTGAATCTGCACTTATCCCCACC
ACCTGGGGACCCCCTTGTTGTGTCCAGGACTCCCCCTGTGTCAGTGCTCTGCTCT
CACCCTGCCCAAGACTCACCTCCCTTCCCCTCTGCAGGCCGACGGCAGGAGGAC
AGTCGGGTGATGGTGTATTCTGCCCTGCGCATCCCACCCGAGGACTGAGGGAAC
CTAGGGGGGACCCCTGGGCCTGGGGTGCCCTCCTGATGTCCTCGCCCTGTATTT
CTCCATCTCCAGTTCTGGACAGTGCAGGTTGCCAAGAAAAGGGACCTAGTTTAG
CCATTGCCCTGGAGATGAAATTAATGGAGGCTCAAGGATAGATGAGCTCTGAG
TTTCTCAGTACTCCCTCAAGACTGGACATCTTGGTCTTTTTCTCAGGCCTGAGGG
GGAACCATTTTTGGTGTGATAAATACCCTAAACTGCCTTTTTTTCTTTTTTGAGG
TGGGGGGAGGGAGGAGGTATATTGGAACTCTTCTAACCTCCTTGGGCTATATTT
TCTCTCCTCGAGTTGCTCCTCATGGCTGGGCTCATTTCGGTCCCTTTCTCCTTGGT
CCCAGACCTTGGGGGAAAGGAAGGAAGTGCATGTTTGGGAACTGGCATTACTG
GAACTAATGGTTTTAACCTCCTTAACCACCAGCATCCCTCCTCTCCCCAAGGTG
AAGTGGAGGGTGCTGTGGTGAGCTGGCCACTCCAGAGCTGCAGTGCCACTGGA
GGAGTCAGACTACCATGACATCGTAGGGAAGGAGGGGAGATTTTTTTGTAGTTT
TTAATTGGGGTGTGGGAGGGGCGGGGAGGTTTTCTATAAACTGTATCATTTTCT
GCTGAGGGTGGAGTGTCCCATCCTTTTAATCAAGGTGATTGTGATTTTGACTAA
TAAAAAAGAATTTGTAAAAAA

FIG. 8a

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILV
HVTDRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISI
RQMAYVSGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTF
WGVVFFDACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLW
AFITAGGSLRSIQRSSCVRTDYLD

FIG. 8b

CCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCCTTCCCACCTGACCAG
CCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTCGCGTTCGGCCCGGCCTT
CGCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTC
GCAGGGGCATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCA
TCTTGGTCCATGTGACCGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGA
TTTTTGGTGCTGCTGTCTCTGTCCTTCTACAGGAGGTGTTCCGCTTTGCCTACTA
CAAGCTGCTTAAGAAGGCAGATGAGGGGTTAGCATCGCTGAGTGAGGACGGAA
GATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTGGTCTCTCCTTCGGTAT
CATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTTGGGCCAGGT
GTGGTTGGGATCCATGGAGACTCACCCTATTACTTCCTGACTTCAGCCTTTCTGA
CAGCAGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATGCCTG
TGAGAGGAGACGGTACTGGGCTTTGGGCCTGGTGGTTGGGAGTCACCTACTGAC
ATCGGGACTGACATTCCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCATCTA
TGCAGTCACTGTTTCCATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCT
CCGAAGTATTCAGCGCAGCCTCTTGTGTAAGGACTGACTACCTGGACTGATCGC
CTGACAGATCCCACCTGCCTGTCCACTGCCCATGACTGAGCCCAGCCCCAGCCC
GGGTCCATTGCCCACATTCTCTGTCTCCTTCTCGTCGGTCTACCCCACTACCTCC
AGGGTTTTGCTTTGTCCTTTTGTGACCGTTAGTCTCTAAGCTTTACCAGGAGCAG
CCTGGGTTCAGCCAGTCAGTGACTGGTGGGTTTGAATCTGCACTTATCCCCACC
ACCTGGGGACCCCCTTGTTGTGTCCAGGACTCCCCCTGTGTCAGTGCTCTGCTCT
CACCCTGCCCAAGACTCACCTCCCTTCCCCTCTGCAGGCCGACGGCAGGAGGAC
AGTCGGGTGATGGTGTATTCTGCCCTGCGCATCCCACCCGAGGACTGAGGGAAC
CTAGGGGGGACCCCTGGGCCTGGGGTGCCCTCCTGATGTCCTCGCCCTGTATTT
CTCCATCTCCAGTTCTGGAC

FIG. 9a

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILV
HVTDRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISI
RQMAYVSGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTF
WGVVFFDACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLW
AFITAGGSLRSIQRSLLCKD

FIG. 9b

CCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCCACCCCCCTTCCCACCTGACCAG
CCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTCGCGTTCGGCCCGGCCTT
CGCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTC
GCAGGGGCATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCA
TCTTGGTCCATGTGACCGACCGGTCAGATGCCCGGCTCCAGTACGGCCTCCTGA
TTTTTGGTGCTGCTGTCTCTGTCCTTCTACAGGAGGTGTTCCGCTTTGCCTACTA
CAAGCTGCTTAAGAAGGCAGATGAGGGGTTAGCATCGCTGAGTGAGGACGGAA
GATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTGGTCTCTCCTTCGGTAT
CATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTTGGGCCAGGT
GTGGTTGGGATCCATGGAGACTCACCCTATTACTTCCTGACTTCAGCCTTTCTGA
CAGCAGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATGCCTG
TGAGAGGAGACGGTACTGGGCTTTGGGCCTGGTGGTTGGGAGTCACCTACTGAC
ATCGGGACTGACATTCCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCATCTA
TGCAGTCACTGTTTCCATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCT
CCGAAGTATTCAGCGCAGCCTCTTGTGCCGACGGCAGGAGGACAGTCGGGTGA
TGGTGTATTCTGCCCTGCGCATCCCACCCGAGGACTGAGGGAACCTAGGGGGG
ACCCCTGGGCCTGGGGTGCCCTCCTGATGTCCTCGCCCTGTATTTCTCCATCTCC
AGTTCTGGACAGTG

FIG. 10a

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILV
HVTDRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISI
RQMAYVSGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTF
WGVVFFDACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLW
AFITAGGSLRSIQRSLLCRRQEDSRVMVYSALRIPPED

FIG. 10b

TTTCCGCGGTGGCCATGACTGCGGCCGTGTTCTTCGGCTGCGCCTTCATTGCCTT
CGGGCCTGCGCTCGCCCTTTATGTCTTCACCATCGCCACCGAGCCGTTGCGTATC
ATCTTCCTCATCGCCGGAGCTTTCTTCTGGTTGGTGTCTCTACTGATTTCGTCCCT
TGTTTGGTTCATGGCAAGAGTCATTATTGACAACAAAGATGGACCAACACAGA
AATATCTGCTGATCTTTGGAGCGTTTGTCTCTGTCTATATCCGAGAAATGTTCCG
ATTTGCATATTATAAACTCTTAAAAAAAGCCAGTGAAGGTTTGAAGAGTATAAA
CCCAGGTGAGACAGCACCCTCTATGCGACTGCTGGCCTATGTTTCTGGCTTGGG
CTTTGGAATCATGAGTGGAGTATTTTCCTTTGTGAATACCCTATCTGACTCCTTG
GGGCCAGGCACAGTGGGCATTCATGGAGATTCTCCTCAATTCTTCCTTTATTCA
GCTTTCATGACGCTGGTCATTATCTTGCTGCATGTATTCTGGGGCATTGTATTTT
TTGATGGCTGTGAGAAGAAAAAGTGGGGCATCCTCCTTATCGTTCTCCTGACCC
ACCTGCTGGTGTCAGCCCAGACCTTCATAAGTTCTTATTATGGAATAAACCTGG
CGTCAGCATTTATAATCCTGGTGCTCATGGGCACCTGGGCATTCTTAGCTGCGG
GAGGCAGCTGCCGAAGCCTGAAACTCTGCCTGCTCTGCCAAGACAAGAACTTTC
TTCTTTACAACCAGCGCTCCAGATAACCTCAGGGAACCAGCACTTCCCAAACCG
CAGACTACATCTTTAGAGGAAGCACAACTGTGCCTTTTTCTGAAAATCCCTTTTT
CTGGTGGAAAAAAA

FIG. 11a

MTAAVFFGCAFIAFGPALALYVFTIATEPLRIIFLIAGAFFWLVSLLISSLVWFMARVI
IDNKDGPTQKYLLIFGAFVSVYIREMFRFAYYKLLKKASEGLKSINPGETAPSMRLL
AYVSGLGFGIMSGVFSFVNTLSDSLGPGTVGIHGDSPQFFLYSAFMTLVIILLHVFW
GIVFFDGCEKKKWGILLIVLLTHLLVSAQTFISSYYGINLASAFIILVLMGTWAFLAA
GGSCRSLKLCLLCQDKNFLLYNQRSR

FIG. 11b

CAGTAATAATACAAAGACAAGATGACGTTGCCCGAGTTCTTTGGCTGCACCTTC
ATCGCCTTCGGACCGCCCTTCGCCTTGTTCGTCTTCACCATCGCCAATGATCCAG
TGCGGATCATCATTCTGATTGCGGCGGCATTCTTCTGGCTGCTTTCCCTGCTGAT
CTCTTCCCTGTGGTATGCCCTGATTCCGCTGAAGGAGTTCCTGGCATTTGGCGTG
GTCTTCTCGGTGTGCTTCCAGGAAGCCTTCCGGTACATCATCTACCGGATACTGC
GCAGCACGGAGCAGGGATTGCACGCCGTGGCGGAGGACACGCGAGTGACGGA
CAACAAGCACATCCTGGCCTATGTCTCCGGCTTGGGATTCGGCATTATATCCGG
GATGTTTGCACTGGTCAATGTGCTGGCTGATATGAGTGGTCCCGGCACCATGGG
CTTGAAGGGCGGAACTGAGCTATTCTTCGTCACCTCGGCTGCCCAGGCGTTGTC
GATTATCCTGCTGCACACCTTCTGGAGCGTTATTTTCTTCAACGCATTCGACACA
AACAACTATATCCACATAGGCTATGTGGTTTTCAGCCACCTGTTCGTCTCCCTGA
TAACTCTGCTCAATGCCAATGAGCTTTACACGACCACTCTGCTGATAAACTACT
TGGTCACCATACTTACGGGAGTCCTGGCCTTCCGGGTGGCTGGAGGAACATCTC
GCAGTTTCAGAAAATTCATAACATGCCAGTAAACATACTCCTAGTATTAACCGC
CT

FIG. 12a

MTLPEFFGCTFIAFGPPFALFVFTIANDPVRIIILIAAAFFWLLSLLISSLWYALIPLKEF
LAFGVVFSVCFQEAFRYIIYRILRSTEQGLHAVAEDTRVTDNKHILAYVSGLGFGIIS
GMFALVNVLADMSGPGTMGLKGGTELFFVTSAAQALSIILLHTFWSVIFFNAFDTN
NYIHIGYVVFSHLFVSLITLLNANELYTTTLLINYLVTILTGVLAFRVAGGTSRSFRKF
ITCQ

FIG. 12b

ATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTCGCGTTCGGCCCGGCCTTCG
CGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTCGC
AGGGTGAGTAGAGGGCCCGGGAGACGCGGGAGAGCGTCGAAGAGAGAGGTGC
GGAAGGGGCTGGAGGAACTGGGGCAAGCCTGGGAGCCTGAATTGGGGACGAT
AAGTCGGAGGTGAAGTTTGGGCGGAGGTGAGGGGTTGGGTCTGGGAGATTTGT
CCTTTCCCGCAGTTGGTTTCCACCTTCCAAGGATCTCACAGATTCCTCCTATATT
CCTCCCAGCGACGTCAGAGAAGGCCCAAGGCCGAGACTCGTGAGGGGGCTGTG
CTGACCTAGGCAGGCCGAGTCAGGTGCCTTAGGGGAGGATCCAGGAACGGATA
CCTCGCCCTTCCGTGCTCGCACACTCTGGCTGTCATCGCTCTGAAGACTCTTTAA
TTAGATTTCTCCCCTTTCCAGTGCGTTCACTTTTCTACAGATGAGTCTCTTGGTG
GAGACAGTTACCCTACCTGGTCCATGTCTCCCTAACCATCCGGAAGGCTAACTT
CCACTTTTCAAGCAGCTTTGGCTGGTTTCCCTCCTTGATTTCTCTGGCTCCCACT
ACTATTGCTTGTCTCACTGCCCCTGTCTTTTCTCAGGGCATTTTTCTGGCTGGTCT
CCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGGTCCATGTGACCGACCGGTC
AGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTCCTT
CTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGTAAGAAGATGGA
GTGGTCTGGAGGGGAGAGGGGCAAAGGACTGCACTATGGGAAGTGGGGCAGC
CCCTGGGTGCTGGTTTGGAAGAGGAGGCACTAAGGGAGGACATTAGAGGGAAA
GGAGCATCCCTGCCCTCCCTCATGTTTCCCCTACCCCACCCCACCCCAGGAAGG
CAGATGAGGGGTTAGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATC
CGCCAGATGGCCTATGGTGAGCCAAGGGAGAGGGACTGGAGGAGGGAGTTGG
ACAGCCCCCTCCTCTAGGGAAGTCTCTAAATATCCACATGTTCTAAGTGGCTTCT
TACTTTCCTTCATCCGTCACTTCCAAAGAAAGTTGGTCTGGAGGGAGAGTAGAT
GTGAAAGAATTGTAACCGGGAATGGGGAGGGGTCAGTGGTGAACAGGCAATAG
TGTGATCTCTGACATTGATGAGATCCTCCCTTCCCCCAGTTTCTGGTCTCTCCTT
CGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTTGGG
CCAGGTGTGGTTGGGATCCATGGAGACTCACCCTATTACTTCCTGACTTCAGGT
AAGATCCACCTTCTATCTAGCCTTTACCCCCCATCCATCCTTGTCCCTGATCTGA
TTTATTGGCCTTCCCTGAGAGACTTCTTTGGCTCAACATCTCAGGAGCCTGGGA
GAAGATCAGGGATGTATCTCCTCCCCATCTCCCTCCCTGCAGCCTTTCTGACAGC
AGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATGCCTGTGAG
AGGAGACGGTACTGGGCTTTGGGCCTGGTGGTTGGGAGTCACCTACTGACATCG
GGACTGGTGAGTTGGAGACAGGGGCCTGAGTTAGGGAGAAAAGCATTTAATGG
TGAGTGGGATGTGGGGGAAAGGGTATCCTCACTTCTTAACATTTTTAACTTACC
TGGGAGGAGGAGGAAAGGTGAGTCTTTCAAGGTCTCTCACCTCAGCATCATTTC
TATCACCTGCTCTGGGGAGGAGGTTGAAAGGATTAGTCAAACTGTAATGCAGA
GGGCCTGAGGTGAGCAGGAGCGGCAGAAACCTTTGAGTTTCTGAGGAGCTGAA
AATCAAAAGTCCCCTTAACCACAAGATGTTGGTGCTCTGAAGGGAAAGACTGG
AGAATTTGAGAGAGATATCTGGGAGTCAGAAAGGTACAGAGAGAATATGGGGA
TTAGGTCGAGGGAGAATCTAATCTCTTTCCTACTCTTACCCTCCTTCCTAGACAT
TCCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCATCTATGCAGTCACTGTTTC
CATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCTCCGAAGTATTCAGCG
CAGCCTCTTGTGTAAGGACTGACTACCTGGACTG

FIG. 13

TTCCCTCCCTTCCCCAGCTGCCCAGTCATGGGGGCTGCTGTGTTTTTCGGATGCA
CCTTCGTCGCGTTCGGCCCAGCCTTCTCCCTTTTCCTGATCACTGTAGCTGGAGA
CCCACTTCGGGTTATCATCCTGGTGGCGGGAGCCTTTTTCTGGCTGGTCTCCCTG
CTCTTGGCTTCTGTGGTCTGGTTCATCTTGGTCCATGTGACAGACCGATCAGATG
CACGGCTCCAGTATGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTCCTTCTACA
GGAAGTGTTCCGTTTTGCTTACTACAAGCTCCTTAAGAAGGCAGATGAGGGCTT
AGCATCACTGAGTGAGGACGGAAGATCACCCATCTCCATCCGACAGATGGCCT
ATGTTTCTGGTCTGTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATT
TTGGCTGATGCACTTGGGCCAGGTGTGGTTGGGATCCATGGAGACTCACCCTAT
TACTTCCTGACTTCAGCCTTTCTGACAGCAGCCATTATCCTGCTCCACACCTTTT
GGGGAGTTGTGTTCTTTGATGCCTGTGAGAGGAGACGGTACTGGGCTTTGGGCC
TGGTAGTTGGGAGTCACCTTCTGACATCGGGACTGACATTCCTGAACCCCTGGT
ATGAGGCTAGCCTGCTGCCCATCTATGCAGTCACCGTTTCCATGGGGCTCTGGG
CGTTCATCACAGCCGGAGGCTCCCTCCGAAGTATCCAGCGCAGCCTTTCGTGTA
AGGACTGACTACCTGGACTGATCGCCCGACAGATCCCATCTGCCTATCCACTGC
CCATGACTGAACCCAGCCCCAGCCCGGGTCCATTGCCCTCATCCTCCGTCTCCTC
GCTGATGTGCCCCGCTTCCTTCCGGGTTTGGCGTTGTCCATTTGTGACCTGTAGT
CTCTAAGCTTTCTCAGGAGCAGCCTGGGTGCAGCCAGTCAGGGACTGGTGGGTT
TGAATCTGCATCTCTCCCCACCACCTGGGGACCCCCTTGTTGTCCAGGTCTCCCC
ATGTGTCAGTGCTCCACCCTCACCCTGCCCATGACTCACCCCGCTTCCCCTCTGC
AGGCCGCCGGCAGGAGGACAGTCGGGTGATGGTGTACTCTGCCCTGCGCATCC
CACCCGAGGACTGAGGGAACATGGGGGGGCCCCTGGGCCTGGGGTGCCCTCCC
GAT

FIG. 14a

MGAAVFFGCTFVAFGPAFSLFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILV
HVTDRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISI
RQMAYVSGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTF
WGVVFFDACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLW
AFITAGGSLRSIQRSLSCKD

FIG. 14b

TTCCCTCCCTTCCCCAGCTGCCCAGTCATGGGGGCTGCTGTGTTTTTCGGATGCA
CCTTCGTCGCGTTCGGCCCAGCCTTCTCCCTTTTCCTGATCACTGTAGCTGGAGA
CCCACTTCGGGTTATCATCCTGGTGGCGGGAGCCTTTTTCTGGCTGGTCTCCCTG
CTCTTGGCTTCTGTGGTCTGGTTCATCTTGGTCCATGTGACAGACCGATCAGATG
CACGGCTCCAGTATGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTCCTTCTACA
GGAAGTGTTCCGTTTTGCTTACTACAAGCTCCTTAAGAAGGCAGATGAGGGCTT
AGCATCACTGAGTGAGGACGGAAGATCACCCATCTCCATCCGACAGATGGCCT
ATGTTTCTGGTCTGTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATT
TTGGCTGATGCACTTGGGCCAGGTGTGGTTGGGATCCATGGAGACTCACCCTAT
TACTTCCTGACTTCAGCCTTTCTGACAGCAGCCATTATCCTGCTCCACACCTTTT
GGGGAGTTGTGTTCTTTGATGCCTGTGAGAGGAGACGGTACTGGGCTTTGGGCC
TGGTAGTTGGGAGTCACCTTCTGACATCGGGACTGACATTCCTGAACCCCTGGT
ATGAGGCTAGCCTGCTGCCCATCTATGCAGTCACCGTTTCCATGGGGCTCTGGG
CGTTCATCACAGCCGGAGGCTCCCTCCGAAGTATCCAGCGCAGCCTTTCGTGCC
GCCGGCAGGAGGACAGTCGGGTGATGGTGTACTCTGCCCTGCGCATCCCACCCG
AGGACTGAGGGAACATGGGGGGGCCCCTGGGCCTGGGGTGCCCTCCCGAT

FIG. 15a

MGAAVFFGCTFVAFGPAFSLFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILV
HVTDRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISI
RQMAYVSGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTF
WGVVFFDACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLW
AFITAGGSLRSIQRSLSCRRQEDSRVMVYSALRIPPED

FIG. 15b

MTLPVFFGCAFIAFGPAFALYLFTIATDPLRVIFLIAGAFFWLVSLLLSSMFWFLVRVI
TNNRDESVQNYLLIFGALLSVCIQELFRLAYYKLLKKASEGLKSINPEEDIAPSMRLL
AYVSGLGFGIMSGVFSFVNTLSNSLGPGTVGIHGDSPQFFLNSAFMTLVVIMLHVF
WGVVFFDGCEKNKWYTLLTVLLTHLVVSTQTFLSPYYEVNLVTAYIIMVLMGIWA
FYVAGGSCRSLKFCLLCQDKDFLLYNQRSR

FIG. 16

GGCCGGCTGCCTTGCCTTTCGAAAGTCAGTTGCGTGCGAGCCGCGAGCGCGAGA
TCATCAAACTGAGAAAGTCGGACTGCGACTCGAAACTGAAATTGAAACTGAAA
GAGAGAAATATTCAAATTGTCGTGTGTGTGGGTGCAAGCAGAGAATATATATCT
CAAGAATATCTGAATACAAGCTCCTGGATTTACGAGCAGCAAAACTAAGTTACC
AATGTGCGAGCCGAAAAAAGCGAGTGAAAAACGTGCGAATATGCCAACTAACT
AAAGACATTTGGATTACAAGAAACCCACGCATTTTGGATTATAAACATTGCGAC
AGGCAGAAAAACCTAAGAATTTCTTCAACGGCGCCAGCATGGAGAACCCAACG
CAGAATGTAAACGAAACCAAGGTGGATTTGGGCCAGGAGAAGGAGAAGGAGG
CGTCGCAGGAGGAGGAGCATGCCACCGCCGTCAAGGAGACCATCATTGACATT
CCCGCCGCGTGCTCCACTTCCTCCAACTCCTCGTCGTACGACACCGATTGCAGC
ACGGCGAGCAGCACCTGCTGCACCCGCCAAGGCGAGCACATCTACATGCAACG
CGAGGCCATCCCGGCCACGCCACTTCCGGAGTCGGAGGATATCGGCCTGCTGA
AGTACGTCCACCGCCAGCACTGGCCCTGGTTCATCCTAGTGATCTCCATCATTG
AGATTGCCATCTTCGCCTACGACCGCTACACAATGCCCGCCCAGAATTTCGGGC
TACCCGTTCCGATTCCGTCGGATTCGGTGCTGGTCTATCGGCCGGACCGGCGTC
TGCAGGTGTGGCGCTTCTTTAGCTACATGTTCCTGCACGCCAACTGGTTCCACCT
GGGCTTCAATATCGTCATCCAGCTGTTCTTCGGCATTCCCCTGGAGGTGATGCA
CGGCACGGCCAGGATCGGCGTGATCTACATGGCGGGCGTTTTTGCCGGATCCCT
GGGCACCAGTGTCGTCGACTCGGAGGTCTTCCTGGTGGGCGCCAGCGGTGGCGT
CTATGCCCTGTTGGCCGCACATCTGGCCAACATCACATTGAACTATGCGCACAT
GAAGAGCGCATCCACGCAACTCGGATCAGTTGTCATCTTTGTCTCCTGCGATCT
GGGCTATGCTCTCTACACCCAATACTTCGATGGAAGCGCCTTCGCCAAGGGTCC
CCAGGTGTCGTACATTGCCCACCTGACGGGAGCCCTGGCAGGACTAACGATCG
GCTTCCTGGTGCTGAAGAACTTCGGTCATCGGGAGTACGAGCAGCTCATCTGGT
GGCTAGCGTTGGGCGTCTACTGTGCCTTCACCGTCTTCGCCATCGTTTTCAACCT
GATCAACACGGTGACCGCCCAGCTGATGGAGGAGCAGGGTGAGGTGATTACCC
AGCATCTGTTGCACGACCTGGGAGTGTCCTAAGTGTGAGGTTCGGAGTCGTCAG
CATGCTCGCAGGGATTCGGAATCTGCTTGAGCTTCAGGAGAGATCGAGAGACA
GAGAGTTGGTGGAAAAGAAAAGTTCACTCAACGATTTAGTTCAAAACTAATTC
GATATTCGTTTGGCTTTTGCTTTTCGTTAGCATTATCTCGTTATCGTTACCGTTTG
CAGTTAAACGTTTCAGTTGCGAAACATAGTACACAAACTCATAAAAAAAAAAAA
CAAATCAAGAGAAATACACTGGACAAAAAAAAAGAGCGAGGAGTGAGGAGAAC
ATAAACCGAAGCCGAAACGTGTAAACAAATGTTGTGATAGAACCAAAGACTGA
ATTTATTTCGCGTGTAAAAACCAAGTAAAAATCAAGAGGAAAATCAAAGAGGA
GAAACAGAACTAATCGCCTCTCGCTATGATTTAAATGAACCCAATTATCCATGT
TTTCAATTAATGGTTTGTCTGTTTTCTTAAATTATGTATTTATTGGCCGCAATTAC
TACGAATGAATCGAATCGAAGCATCAGCAAACTGTATCAAATTGTTTATACATC
CATAAGCATAATGTGCTCCGAATTGTAGGATTAGTGTTATAATTTATATATATTT
AGGTATAACTAGCCCTCCTAACAAATTGTTTCAAATTGTAAATACTATTAAGTC
GCACACTAGTCAAACAACAACAACAGCAACAGCAAAAACAACAAAAAATGTAT
GGAAAACCACAGCAAAGAACCATTCAATTCAGATCAATTAAGCAAATCGAGTT
AAATTAAATTAAATTATACTAAAGTCACTTAATGCGTTACAAAATCGAGCAAAT
ATTTATCGTAATCCCTACACACACACACACACACACTCGAAAGTATTACTAATT
ATATTTATTTATGGTAGGGCAGCGAGGGTTTATTAATTCGTCAATTGAGCGAAC
TATTTATTTATTTATTTATTTAATAATTTAGTGAAATTCACACAAACAAGCACGA
AAAAACAACAACAACACAAGAGAGAGAAGAAACAAACCAATTCAACTGTAAA
AATATCCAATTGAAAAATACACACGAAAAGCCAAAGAAAATAAAAAATCAAA
ACATTTCAAGAATACAACAGTAATAACAAAATACAAAAAA

FIG. 17a

MENPTQNVNETKVDLGQEKEKEASQEEEHATAVKETIIDIPAACSTSSNSSSYDTDC
STASSTCCTRQGEHIYMQREAIPATTLPESEDIGLLKYVHRQHWPWFILVISIIEIAIFA
YDRYTMPAQNFGLPVPIPSDSVLVYRPDRRLQVWRFFSYMFLHANWFHLGFNIVIQ
LFFGIPLEVMHGTARIGVIYMAGVFAGSLGTSVVDSEVFLVGASGGVYALLAAHLA
NITLNYAHMKSASTQLGSVVIFVSCDLGYALYTQYFDGSAFAKGPQVSYIAHLTGA
LAGLTIGFLVLKNFGHREYEQLIWWLALGVYCAFTVFAIVFNLINTVTAQLMEEQG
EVITQHLLHDLGVS

FIG. 17b

CCAGAAAGCAAAATAGAAACAAATTTTCCATATTTCATGCTAAATTGGCACAGA
TCCGTACTACTATGCTCATGAGTCGAGCGCTTTGCCGGAGCTGGCTACCCCAGG
TGGCCCGCAGATGTCATGCTAATGTGAATGTGCCAATCCTGCGGATAAACTCTG
GTCATCCGGCGGCGAGGTCATGTCGGCAGATTCACAGCAACCGAAAACAGAGC
AGCAACCTGAAGCCGACGACTGGGGAGCCTGCGGCAGCGGAGCAGAACACCCC
GGTGCCGGTGAACAATGTGATCAAGGCGGTGGCCTTCACGGGAGCATTTACGG
TCGGCTGCTTTGCGGGTGCCACCATCCTGGAGTACGAGAACACACGTAGCCTAA
TCCTAGAAAAGGCTCGCCAGGCGAGATTCGGTTGGTGGCAGAGTCGTTCGCTGG
CGGACAGGGATTACTGGACACAGATCAAACAAGACATCCGGCGGCACTGGGAC
TCACTGACACCCGGCGACAAGATGTTTGCTCCTATCTTACTCTGCAATTTGGTGG
CCTTCGCCATGTGGCGGGTGCCCGCTCTGAAATCCACAATGATTACCTACTTCA
CATCCAATCCAGCGGCGAAAGTCGTCTGCTGGCCCATGTTCCTGTCCACATTCA
GCCATTACTCGGCTATGCACCTTTTCGCCAATATGTACGTGATGCACAGCTTTGC
CAACGCTGCGGCTGTATCGTTGGGTAAAGAGCAATTCTTAGCGGTCTACCTCAG
CGCCGGCGTCTTCTCCAGTCTGATGAGCGTGCTCTACAAGGCGGCCACGAGTCA
GGCGGGGATGTCCCTGGGTGCGTCTGGAGCTATAATGACACTGCTGGCCTATGT
ATGCACCCAGTATCCGGACACACAACTTAGCATTCTCTTTCTACCCGCGTTGAC
ATTCTCCGCTGGAGCTGGTATTAAAGTGCTAATGGGCATCGACTTTGCTGGCGT
CGTGATGGGCTGGAAGTTCTTCGATCACGCAGCGCATTTGGGCGGCGCCATGTT
TGGCATCTTTTGGGCCACGTATGGGGCACAGATATGGGCAAAGCGCATTGGTCT
ACTGAATTACTACCATGACCTGCGCCGGACGAAGCAGAAATAG

FIG. 18a

MLMSRALCRSWLPQVARRCHANVNVPILRINSGHPAARSCRQIHSNRKQSSNLKPT
TGEPAAAEQNTPVPVNNVIKAVAFTGAFTVGCFAGATILEYENTRSLILEKARQARF
GWWQSRSLADRDYWTQIKQDIRRHWDSLTPGDKMFAPILLCNLVAFAMWRVPAL
KSTMITYFTSNPAAKVVCWPMFLSTFSHYSAMHLFANMYVMHSFANAAAVSLGK
EQFLAVYLSAGVFSSLMSVLYKAATSQAGMSLGASGAIMTLLAYVCTQYPDTQLSI
LFLPALTFSAGAGIKVLMGIDFAGVVMGWKFFDHAAHLGGAMFGIFWATYGAQI
WAKRIGLLNYYHDLRRTKQK

FIG. 18b

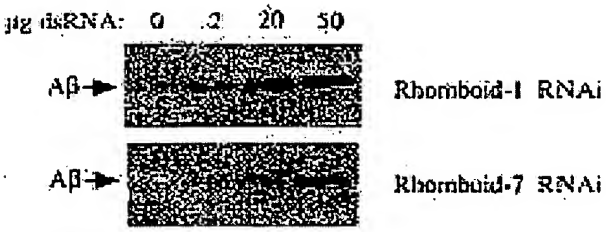


FIG. 19